A NEW LOOK TO ELECTRONIC BANDOLIER

Many who read *Bandolier* in its paper version with a cup of coffee also appreciate the fact that it exists on the Internet, both as a resource for things half-forgotten, and because the Internet version contains much more than appears on paper.

The *Bandolier* Internet site is now visited about seven million times a year and many more times on mirror intranet sites. For most people *Bandolier* is the Internet site. Over the next few months the Internet site is going to change to make it more user-friendly, and better reflect the preponderance of electronic readers.

The reasons people use electronic *Bandolier* are also changing. Many will be professionals in the UK and almost every other country in the world. Personal or practice development plans are being widely adopted, and the reorganisation should facilitate the use of *Bandolier* in fulfilling those plans. A simple structure will also help lay people trying to find high-quality information on the Internet.

New home page

The new home page will have the same address as now (www.ebandolier.com, or www.jr2.ox.ac.uk/Bandolier). The home page will now direct you to one of four new areas to help navigate around.

What's New

Regular visitors want to know what has been added since their last visit, either in the journal (the electronic version of the monthly paper issue) or in other parts of the site. The **What's New** page will tell them that. It will be an access point for all electronic issues of *Bandolier* and *ImpAct*. It will also be the access for facsimile versions of the journal (PDF, or portable document formats) which allow copies of the journal to be printed out from your own computer. The Spanish language edition, *Bandolera*, will also live here.

Bandolier Knowledge

One of the electronic successes over the last two years has been the growth in the number and extent of resource centres that gather together good knowledge on a topic. Currently there are 33 of these. There is a limit to how much can sensibly be kept even on an electronic page. Some of these will therefore be split and others added, so that the number will increase to 50 quite rapidly, and will grow beyond that.

Bandolier Extra

Another success has been the creation of Web Essays, Internet lectures in effect. Hundreds of copies of these are read and printed every week. To make it easier, especially for those working on their personal development plans, these will be turned into downloadable PDFs under the title of *Bandolier Extra.*

New essays and reviews will be created. As a first example, a review of the effect of NSAIDs on bone first appeared in November, and an updated version appears in December. Combined with the downloadable **What Is** series of articles, this will be an important learning resource.

About us

In a world increasingly (and rightly) paranoid about unseen bias, Internet visitors should know who produces material on the site and how it is funded. That's already there on the *Bandolier* site, but as things develop or change we will seek to find ways of making it more transparent.

And finally

Bandolier prides itself on its relations with readers to ensure that it gives them the knowledge they want in the way that they want it. If you want to let us know what you think, or register for a monthly email alert about What's New, send an email to bandolier@pru.ox.ac.uk.

A number of organisations have also asked about having a *Bandolier* mirror on their own intranets. We are finding ways of accommodating this, and if you are interested send an email to Maureen at maureen.woodford@pru.ox.ac.uk.

The views expressed in Bandolier are those of the authors, and are not necessarily those of the NHSE

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ANTICOAGULATION FOR AF: RCTS VERSUS CLINICAL PRACTICE

The number one frequently asked question in evidence-based medicine is "are the results of clinical trials applicable to clinical practice?" One of those simple questions for which simple answers are infrequently available from actual evidence. Because clinical trials often test a single technology and have defined inclusion and exclusion criteria, it can seem as if they could never apply to a clinic of octogenarians all with several other diseases.

It is unusual to have results from a meta-analysis of randomised trials compared with results of clinical practice, but for anticoagulation a group from London have turned up trumps [1], and another from Glasgow provide useful information about anticoagulation in the elderly [2].

Study

The main study [1] sought prospective cohort or retrospective case note reviews of anticoagulation for atrial fibrillation in clinical practice. Patients had to be in ordinary clinical practice settings unrestricted by age or other considerations. Anticoagulation had to be conducted in routine, not research, settings, and there had to be longitudinal data on stroke rates and haemorrhagic complications. Data from such studies was to be compared with a meta-analysis of randomised controlled trials.

Results

There were three eligible clinical practice studies performed in the USA, Canada, and England. They all had similar definitions for atrial fibrillation, risk, criteria for anticoagulation and for outcomes. In all there were 410 patients with 842 years of follow up, compared with 1225 patients and 1889 patient years in randomised trials.

Compared with randomised trials, patients in clinical practice were older, were more likely to be women, and have diabetes, previous stroke or heart failure, but less likely to have ischaemic heart disease.

Rates of ischaemic stroke, intracranial haemorrhage and major bleeding were similar for clinical practice and clinical trials (Figure 1). Minor bleeding occurred more frequently in clinical practice, though individual study rates varied markedly. Including an additional study on institutionalised patients with higher stroke and bleeding events did not change the overall conclusion.

Older versus younger patients

A retrospective follow up study in Glasgow [2] would not have fulfilled all the inclusion criteria for clinic studies in the London review, but was close. For instance, it recruited patients aged 60-69 years and those older than 75 years, but not in between.

It had 328 patients with 180 years of follow up, with similar average age but many more women than the randomised trials. There were two ischaemic strokes (1.1 per 100 patient years), four intracranial bleeds (2.2/100), five major bleeds (2.8/100 patient years) and four minor bleeds (2.2/100). The major difference was an excess of intracranial bleeds compared to the other practice studies and trials.

Analysis was by those aged 60-69 years (204 patients) and the 124 older than 75 years. There was no difference in number of high INRs, out of target INRs, INRs above 7 and haemorrhages in the two age groups. Two ischaemic strokes occurred in older women. Short duration follow up of less than 12 months was associated with more INR values above 7 and more haemorrhages.

Comment

Confidence that clinical trial results translate to clinical practice is important in implementing therapy, and fulfilling guidelines and service frameworks. People want to know that what they are doing for their patients will benefit them. Here we have evidence that a wet Thursday in Grimsby is much the same as anywhere else when it comes to using anticoagulation for atrial fibrillation. Older patients do as well as younger ones.

References:
1   A Evans, L Kalra. Are the results of randomized controlled trials on anticoagulation in patients with atrial fibrillation generalizable to clinical practice? Archives of Internal Medicine 2001 161: 1443-1447.
2   M Copland et al. Oral anticoagulation and hemorrhagic complications in an elderly population with atrial fibrillation. Archives of Internal Medicine 2001 161: 2125-2128.

Figure 1: Major events in clinical practice and clinical trials of anticoagulation for AF
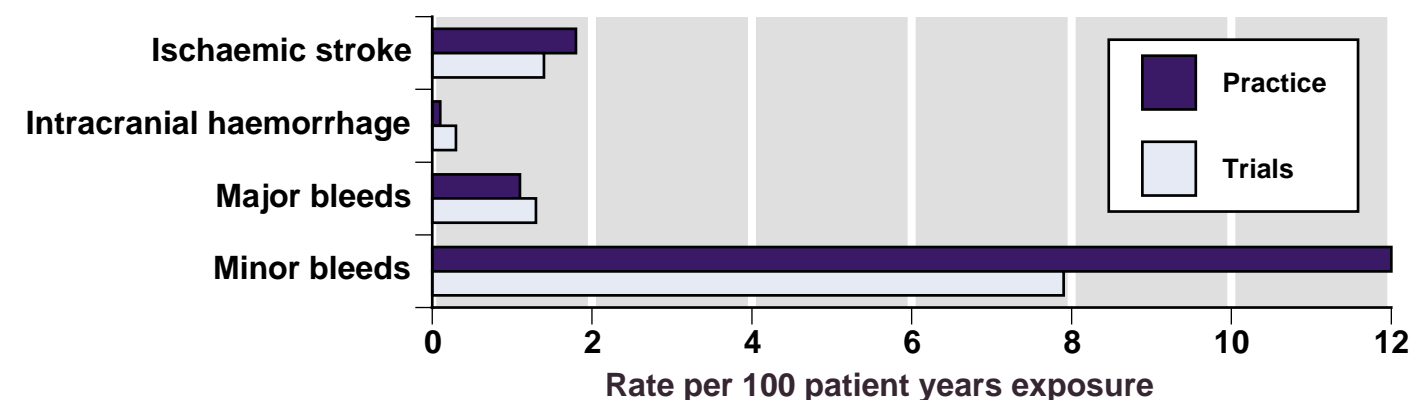
NSAIDs AND FRACTURE RISK

Laboratory exploration of the effect of NSAIDs on bone metabolism has demonstrated that bone resorption can be affected through prostaglandin inhibition. One implication is that NSAIDs potentially could reduce bone loss and hence fracture risk. A huge observational study using the UK general practice research database (GPRD) [1] tells us that this hope will not be realised.

Background

A large study of aspirin and NSAID use on bone mineral density in 7,768 white women older than 65 years in the USA [2] concluded that bone mineral density was higher in users of these drugs. Risk of fracture was unaffected. The study had the benefit of being large, but aspirin and NSAID users were different from non-users. Osteoarthritis, rheumatoid arthritis, back pain and other conditions were much more common in NSAID users than nonusers. Adjustment of results for potential confounding can be difficult in circumstances where subjects and controls differ markedly.

NSAID use did not affect the rate of excretion of markers of bone resorption [3], but bone mineral density at some sites was again found to be affected by proprionic acid NSAIDs in 84 older women [4].

The background evidence that NSAIDs reduce fracture risk was thin, but the apparent effects on bone density meant that some reduction in fracture risk might be expected. A very large study would be needed to show this.

Study

The large retrospective cohort study was conducted using the GPRD [1]. It looked at fracture risk in people using NSAIDs and compared that with people who did not use NSAIDs.

NSAID users fulfilling one or more prescriptions for an NSAID from 1987 up to end 1997 were included, and divided arbitrarily into those receiving three or more prescriptions and those receiving one or two prescriptions. A control group of people never having a prescription for NSAIDs was created by matching for sex, age, and practice (where possible). Systemic corticosteroid use was an exclusion criterion for users and controls. Information on about a dozen possible confounding conditions, and about a dozen possible confounding drug treatments was collected for each case and control.

After a prescription was filled follow up was until fracture or 91 days after the last prescription. Nonvertebral fractures were assessed by ICD codes and vertebral by radiography.

Results

NSAIDs were prescribed for 501,000 patients, with 215,000 having three or more prescriptions for a median 3.4 years (regular users), and 287,000 having one or two prescriptions for a mean of 0.7 years (incidental users). There were 215,000 controls. Back pain and rheumatoid arthritis were more common in NSAID users than in controls. Incidental users were about 10 years younger than the mean age of 54 years for regular users and controls.

Nonvertebral fractures occurred more frequently in older women and the oldest men (Figure 1). For women fracture rates rose substantially after age 64.

Fracture rates with regular NSAID users were certainly not lower than controls. If anything, they were somewhat higher (Table 1) for vertebral and all nonvertebral fractures. Regular users had fracture rates no different from incidental users. No NSAID was associated with higher or lower rates of fracture. Restricting analysis to patients with a history of arthopathy reduced the difference between regular users and controls for nonvertebral fractures, with a relative risk of 1.2 (1.1 to 1.3).

Figure 1: Annual incidence of nonvertebral fractures in men and women by age in 215,000 UK GP patients not prescribed NSAIDs

Annual incidence of nonvertebral fracture (%)
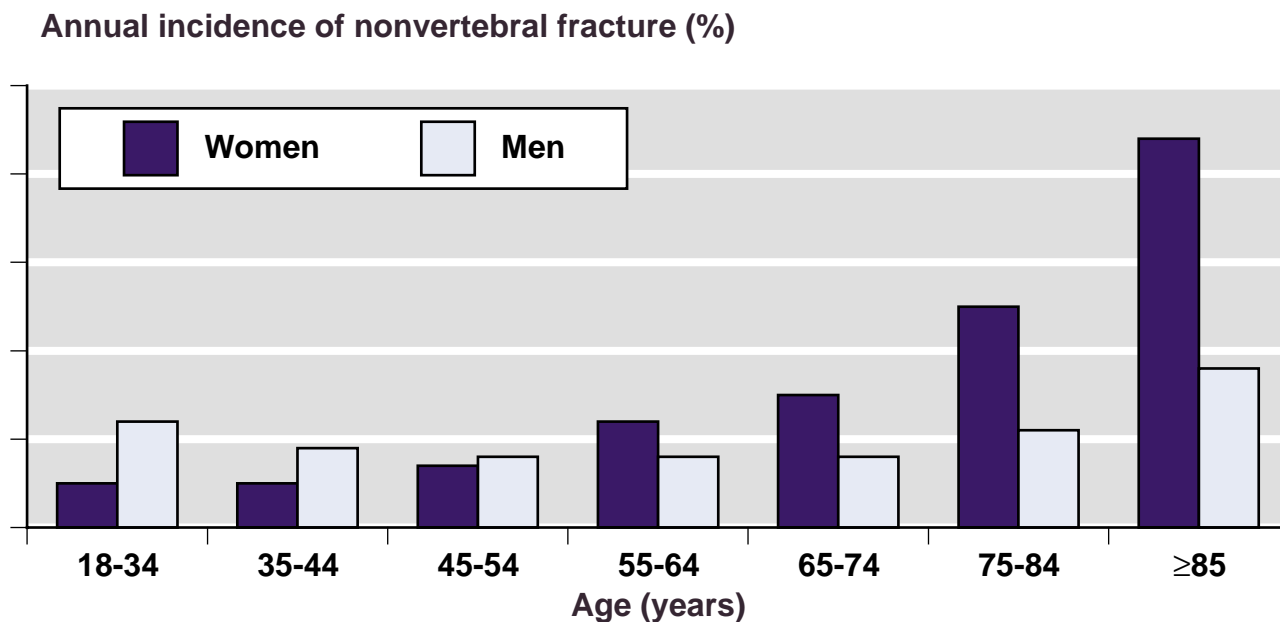
Table 1: Occurrence and relative risk of regular NSAID users (215,000) and non-NSAID controls (215,000) in UK general practice

Fracture type	Regular NSAID user		Control		Relative risk (95%CI)
	Number of fractures	Rate per 100 years	Number of fractures	Rate per 100 years	
Vertebral	808	0.1	192	0.03	2.9 (2.5 to 3.4)
All nonvertebral	10505	1.5	5793	1	1.5 (1.4 to 1.5)
Forearm	2516	0.3	1556	0.3	1.3 (1.2 to 1.4)
Hip	973	0.1	686	0.1	1.1 (0.98 to 1.2)

Comment

This beautiful study tells us that there is no major effect of NSAIDs on risk of fracture. It also shows the problems with confounding. While many confounding factors could be taken into account, others, like diet, exercise or bone density could not. To properly take account of confounding factors you have to know what they are, and how much to adjust for them.

The impact of NSAIDs on bone metabolism, on fractures, and bone healing has become a hot topic. *Bandolier* has reviewed all the evidence available. This can be seen on the *Bandolier* Internet site, either to be read on-screen, or downloaded as a printable document (*Bandolier Extra*).

References:
1   TP Van Staa et al. Use of nonsteroidal anti-inflammatory drugs and risk of fractures. Bone 2000 27: 563-568.
2   DC Bauer et al. Aspirin and NSAID use in older women: effect on bone mineral density and fracture risk. Journal of Bone and Mineral Research 1996 11: 29-35.
3   NE Lane et al. Aspirin and nonsteroidal antiinflammatory drug use in elderly women: effects on a marker of bone resorption. Journal of Rheumatology 1997 24:1132-1136.
4   DJ Morton et al. Nonsteroidal anti-inflammatory drugs and bone mineral density in older women: the Rancho Bernado study. Journal of Bone and Mineral Research 1998 12: 1924-1931.

WARTS AND ALL

Not many people know that Oliver Cromwell had Welsh descendants, and had his grandfather not taken his grandmother's surname on marriage, he would have been known to posterity as Oliver Williams. Most people know he had a large wart on his face. Treating warts has always been of interest to *Bandolier*, it being one of those common conditions for which knowledge about effective treatments seems to be sparse. When a Cochrane review [1] comes up not only with some answers on available treatments, but much common sense about trial methodology, applause is in order.

Review

The review had some ambitious aims to examine not only all available treatments, but also to examine trial evidence for clinically useful information, like differences between hands and feet, or untreated versus previously treated warts. In many of these reviewers were thwarted by lack of good evidence. As expected from a Cochrane review searching and basic methods were excellent. The criteria for a valid clinical trial of warts were addressed in a thoughtful way.

Results

There were 49 randomised trials for inclusion. In general their methodological quality was poor, with 38 classified as low quality (allocation method, blinding and withdrawals not described) and only two as high quality (allocation method, blinding and withdrawals described, intention to treat analysis). Nine trials had intermediate quality.

Being definite about results from this data set could never be easy. The reviewers' conclusions are shown in Table 1. Topical salicylates were compared with placebo in six trials on non-refractory warts (Figure 1), and the NNT was 3.7 (2.7 to 5.5). Aggressive cryotherapy was compared with gentle cryotherapy in four trials (Figure 2) and the NNT was 4.7 (3.4 to 7.3). There was some evidence for topical dinitrocholorobenzene, but from tiny numbers.
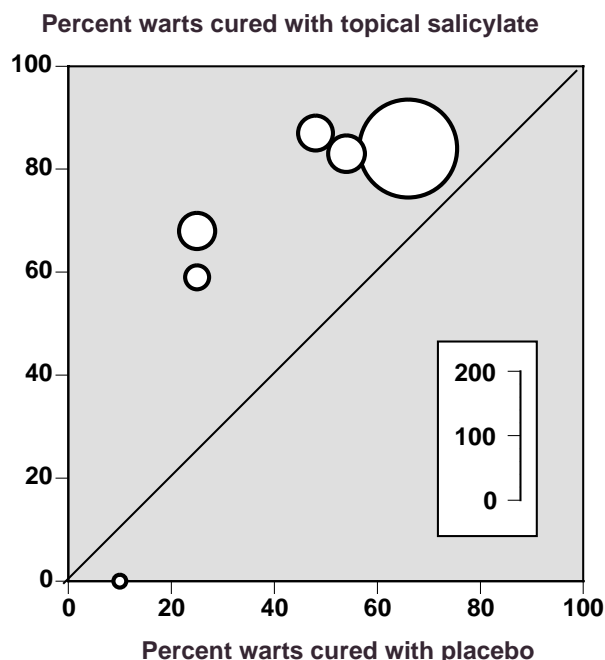
For many other treatments, including lasers, imiquimod, surgery, aldehydes, podophyllin, podophyllotoxin, cantharidin and silver nitrate, there was little or no published evidence.

Comment

Does this help? It confirms that for commonly used treatments we have the best of what little evidence is available, and at least we know that we are not missing something. Most important is that we have only two (2) high quality trials about wart treatment, a common enough condition that is a source of much angst.

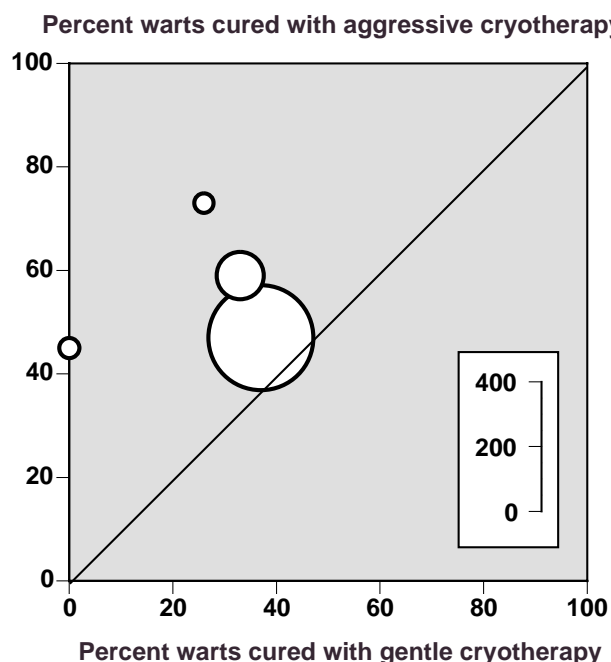## Table 1: Main results of review of cutaneous wart treatments

Treatment	Number of trials	Reviewer conclusions
Topical salicylic and/or lactic acid	13	Six trials had placebo comparison. 75% of 191 patients cured with treatment and 48% of 185 with control. NNT 3.7 (2.7 to 5.6)
Cryotherapy	16	Four trials compared aggressive versus gentle cryotherapy. 52% of 304 patients cured with aggressive treatment and 31% of 288 with gentle treatment. NNT 4.7 (3.4 to 7.3)
Intralesional bleomycin	5	Insufficient evidence of efficacy. No difference between bleomycin and placebo in two trials
Topical 5-fluorouracil	2	Some evidence of efficacy, but not discernably better than other, simpler, treatments
Intralesional interferons	6	Insufficient evidence of efficacy, including no difference between IFN alpha and placebo, and higher adverse events
Topical dinitrochlorobenzene	2	80% cure in 40 treated patients and 43% of 40 with placebo. NNT 2.7 (1.8 to 5.6). Some evidence of efficacy but tiny numbers
Photodynamic therapy	4	Pooling impossible because of different regimens, but some evidence of efficacy

Figure 1: Wart cures with topical salicylate and placebo

Percent warts cured with topical salicylate

Percent warts cured with placebo

Figure 2: Wart cures with aggressive and gentle cryotherapy

Percent warts cured with aggressive cryotherapy

Percent warts cured with gentle cryotherapy

The review is brilliant in how it picks apart the relevant issues for performing wart trials in future. These include variables associated with participants (age, site and type of lesion, history of treatment) and treatments (including trial duration). No new trial should be undertaken without reference to this review. Some new trials (and new treatments?) are needed to better inform current and future treatment.

References:
1   S Gibbs et al. Local treatments for cutaneous warts (Cochrane Review). In: The Cochrane Library, Issue 4, 2001. Oxford: Update Software.

BOTULINUM TOXIN FOR MIGRAINE PREVENTION

A randomised trial tells us that botulinum toxin injected into the forehead reduces migraine frequency or intensity [1]. How are we to interpret this? Is it the best thing since sliced bread, or does the evidence leave us with that "ho..hum" feeling?

The first thing to do is ask what criteria are important for clinical trials of migraine prophylaxis. A review that draws heavily on the work of others helps thinking [2] because it examines important issues about trial design. Trials should meet several critical criteria, some obvious, some less so:

♦ They should make sure that the diagnosis of migraine is done properly, to exclude other forms of headache.
♦ Migraine frequency can increase secondary to treatment overuse, so making sure that patients do not have drug-induced medication becomes mandatory. There should be a sensible washout period before treatment starts.
♦ A washout period allows the collection of diary records about the frequency and severity of migraines before treatment begins. Four weeks after discontinuation of drugs is sensible.
♦ A minimum number of migraines per month should be imposed, and three per month is an arbitrary minimum.
♦ The duration of the study should be long enough for effects of treatment to become fully apparent; three months is suggested.
♦ Adverse effects may be seen early, but full benefits later, and titration of dose to effect may be necessary to reduce dropouts and make intention to treat analysis fair.

There may be other considerations for different treatments, but, simply put, trials lacking these characteristics should be treated with caution.

Botulinum toxin RCT

Trial design

The trial was randomised, double blind and compared placebo with two strengths of botulinum toxin over three months. We are told that non-completers were dismissed from the study, but not how many or what treatment. The trial would score 2 out of a possible 5 points on a common quality scoring scale in which trials scoring 2 or less may be subject to bias.

Adult patients had to have migraine diagnosed to International Headache Society criteria, with 2-8 episodes a month of at least moderate severity over a four-week baseline period. Patients could continue using concurrent prophylactic medicines. Exclusions were sensible, and included more than 15 headache days a month, and symptomatic medication overuse.

Treatments were injections of placebo vehicle, or 25U or 75U symmetrically into the forehead muscles. Follow up was over three months, during which patients kept diaries, including migraine frequency and intensity. Assessments were made at one, two and three months

Results

There were 123 participants with 122 completers. Migraine frequency averaged 4.0 to 4.8 per month in the three groups. Baseline severity was the same.

For the favoured outcome of reduction in migraine frequency, statistical differences occurred only with 25U at three months, but not with 25U at one or two months, or with the higher dose of 75U at any time. Results were given for 50% reduction in migraine frequency or reduction in frequency of two episodes a month. Formal statistical significance was barely attained, with a p value of 0.46, though the relative risk included 1 (Table 1). Different results in one or two patients would have rendered the result non-significant (Table 1).

For the secondary outcome of migraine severity, statistically significant benefit was attained for 25U at one and two months, but not at three months, and not at any time for 75U.

Adverse events occurred more frequently with 75U (50% of patients) than with placebo (25%), and we are told that with 25U the rate was not significantly different from placebo.

Comment

There was a dose response for adverse events, with higher rates with 75U. This dose at no point or with any endpoint

Table 1: Migraine frequency - 25U botulinum toxin and placebo. Effect of a single patient change in success (treatment or placebo groups) on results

| | At least 50% reduction in migraine frequency | | |
| | Number/Total | | |
	Botulinum toxin	Placebo	Relative risk (95% CI)
Actual results	19/42	10/41	1.9 (0.98 to 3.49)
One fewer with treatment	18/42	10/41	1.8 (0.93 to 3.35)
One more with placebo	19/42	11/41	1.7 (0.92 to 3.10)

showed a benefit compared with placebo. The 25U dose was only effective on migraine frequency, and then barely, at three months. On migraine severity statistical significance, again bare, was at one and two months.

The simple fact is that with one or two patients giving different responses, this would have been declared a negative trial. It does not inspire confidence, especially as this is the only randomised controlled trial for this intervention in this indication and the quality of reporting allows for the possibility of bias, as well as it being financed by the manufacturer. Given the not inconsiderable expense, justifying this to any purchasing authority would be a hard task.

The trial fulfilled most or all of the criteria for prophylactic interventions in migraine. The intervention just didn't make the grade.

References:
1   S Silberstein et al. Botulinum toxin type A as a migraine preventive treatment. Headache 2000 40: 445-450.
2   V Limmroth, MC Michel. The prevention of migraine: a critical review with special emphasis on beta-adrenoceptor blockers. British Journal of Clinical Pharmacology 2001 52: 237-243.

TONSILLECTOMY: BLEEDING AND PREDICTION

Tonsillectomy is a common operation, and in by far the majority of cases is carried out without any complications. One of concern is postoperative bleeding. In the first 24 hours it is an immediate consequence of operation, but it can occur after the immediate postoperative period and up to 10 days after operation. Tonsillectomy in countries like the UK is now complicated by the need for disposable equipment because of fear of spreading prion diseases.

Could postoperative bleeding be predicted by preoperative tests of abnormal coagulation? A meta-analysis tells us that this is unlikely [1], and has the additional benefit of giving good information on postoperative bleeding rates.

Review

The review used wide searching strategies including the Cochrane Library to find studies examining tonsillectomy and bleeding, with an additional criterion of coagulation tests in people who bled postoperatively. It is not clear that the studies had to conduct preoperative coagulation tests in all patients.

Included studies were those reporting on people undergoing tonsillectomy and/or adenoidectomy, that were prospective, and had groups without concomitant illness. Information obtained was on the end point of bleeding with normal or abnormal coagulation tests.

Results

There were no randomised trials, but four prospective studies with 3384 patients fulfilled the criteria, and six retrospective studies with 8988 patients were included for sensitivity analysis.

The bleeding rate was 3.4% (116/3384; 95% CI 2.8% to 4.0%) in prospective studies and 2.3% (207/8998; 95% CI 2.0% to 2.6%) in retrospective studies. Overall it was 2.6% (323/12.372; 95% CI 2.3% to 2.9%). Smaller studies were more variable (Figure 1). Bleeding was usually delayed, but this was not always specified.

In 323 patients who bled, abnormal coagulation tests were found in 24 (7.4%, 95% CI 4.6% to 10.3%), and identical rates were found in prospective and retrospective studies.

Comment

Readers will need to take this paper slowly. As best **Bandolier** can judge, of the 12,372 patients 323 bled, and coagulation tests are given on these only. The papers did not use universal preoperative screening. This is important because the paper reports sensitivity, specificity and positive and negative predictive values. For analysis after the event, these are unhelpful. We do not know how many people had normal or abnormal coagulation tests and did **not** bleed. It is a good example for critical appraisal of diagnostic tests, though.

Figure 1: Bleeding rate in tonsillectomy. Dark symbols prospective studies, light retrospective

Number of tonsillectomies
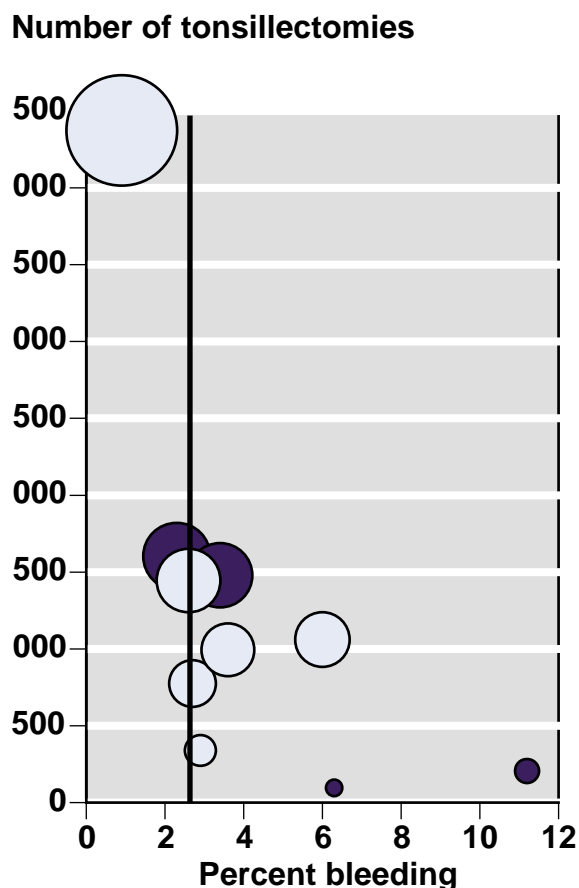
But in reality the low rate of abnormal tests among the very few patients who did bleed absolves us from the need to think about this further. The results cannot get better with universal preoperative screening, and that is helpful in that it makes the result a pretty positive negative.

The most useful aspects of the study may lie in the light it sheds on variability of bleeding rates. Case mix and surgical competence will be important determinants, but one cannot get over the random play of chance. Two prospective and one retrospective study had bleeding rates of over 6%. The two prospective studies had about 100 and 200 patients respectively.

Suppose this was an audit? Would the immediate reaction be to:

1   Blame the surgeon(s)?
2   Blame the hospital?
3   Blame the government?
4   Blame the small sample size?

We need to have a much better handle on the last before we start thinking about one of the first three.

References:
1   P Krishna, D Lee. Post-tonsillectomy bleeding: a meta-analysis. Laryngoscope 2001 111: 1358-1361.

MINDSTRETCHER:
BLIND LEADING BLIND

Continually challenging what constitutes good evidence is a good thing. It keeps us on our toes, it reminds us of our foibles, and we may have missed something. Given that the keystone of good evidence is the randomised, double blind trial, a challenge that claims them to be improperly conducted and open to bias is a serious matter.

This thought provoking assertion [1] comes from people with backgrounds in behavioural science and mathematical psychology. Hardly everyday knowledge, this, so it deserves our attention.

Argument

The argument goes something like this. Suppose doctors or nurses involved in a trial see that some patients are doing well, or badly. Even though the trial is randomised and properly blinded, their beliefs and expectations about the results of the trial are consequently influenced. Their beliefs could influence others concerned with the trial, or the patients. Subtle and even unconscious cues imparted to professionals or patients could influence professionals or patients in making assessments, or interpreting the results.

These unconscious feedbacks could also occur between patients in some circumstances, and true blinding could be lost. Since lack of blinding is known to impart bias, then the trial could become unblinded, even partially. The result would then be a trial in which the quality we seek from randomised double blind trials would be lacking.

For example, if we were comparing an analgesic and placebo in acute pain, a good analgesic might influence a nurse to encourage patients, while a poor analgesic might influence the same nurse to discourage them. A consequence of this would be for placebo responses to vary with the quality of the analgesic under test. Trials of good analgesics would have higher placebo responses than poor analgesics. It has been said that placebo is 55% as effective as the analgesic used [2].

Placebo and acute pain

Two common misconceptions are that a fixed fraction (one third) of the population responds to placebo, and that the extent of the placebo reaction is also a fixed fraction (again about one third of the maximum possible [3]). As Wall points out, these ideas stem from a misreading of Beecher's work of forty years ago [4].

When placebo controls are used in randomised, parallel-group, double-blind, trials in similar clinical settings measuring the same outcome over the same period they would be expected to give about the same overall placebo response. They do not, as Beecher's data showed [3].

The answer

It comes in two parts. Firstly, an apparent correlation between placebo effect and extent of response to analgesic results from using mean values of highly skewed data. When medians are used, the relationship disappears [5]. The second argument is one of size. In a comparison of about 12,000 patients given placebo in acute pain studies, 18% of patients had at least half pain relief over 4-6 hours. In over 50 meta-analyses of identical trials only when there were about 1,000 patients was this accurately measured [6]. With a smaller sample the variability was huge.

Comment

In one clinical area we can be reasonably sure that we are safe, and that leakage of blinding is unnecessary. But it is an important consideration that needs thinking about.

References:
1   MD Kirk-Smith, DD Stretch. Evidence-based medicine and randomized double-blind clinical trials: a study of flawed implementation. Journal of Evaluation in Clinical Practice 2001 7: 119-123.
2   FJ Evans. The placebo response in pain reduction. In: Bonica JJ, ed. Advances in Neurology, Vol 4. New York: Raven Press; 1974:289-296.
3   HK Beecher. The powerful placebo. JAMA 1955 159:1602-6.
4   PD Wall. The placebo effect: an unpopular topic. Pain 1992 51:1-3.
5   HJ McQuay et al. Variation in the placebo effect in randomised controlled trials of analgesics: all is as blind as it seems. Pain 1996 64:331-335.
6   RA Moore. Understanding clinical trials: what have we learned from systematic reviews? Proceedings of the 9th World Congress on Pain, Progress in Pain Research & Management, Vol 16, Eds M Devor, MC Rowbotham, Z Weisenfeld-Hallin. IASP Press, Seattle, 2000, 757-770.